REMARKS

The Claim Amendments

Claims 1, 3, 13-21, 30, and 31 have been amended and claims 2, 4-12, and 22-29 have been previously canceled. Claim 32 has been canceled with this amendment. New claims 33-35 have been added. Applicant has amended claim 1 so that it is drawn to a chemically modified nucleic acid molecule having the following features: (1) it comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; (2) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length; (3) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a human huntingtin (HD) RNA sequence comprising SEQ ID NO: 3578; (4) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human HD RNA; (5) about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2′-O-methyl, 2′-deoxy-2′-fluoro, 2′-deoxy, phosphorothioate and deoxyabasic modifications; and (6) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2′-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2′-deoxy-2′-fluoro pyrimidine nucleotides.

Amended claim 1 is fully supported by the specification as filed, for example, inter alia, at pages 10, 13, 14, 17-19, 22-23, 31-34, and 40-43, as well as. SEQ ID NO: 3578 is the HD sequence of GenBank No. NM_002111. GenBank No. NM_002111 is described in Table I on page 141. Support is also found in the priority documents. U.S. Provisional patent application Nos. 60/363,124 (see, page 10, lines 3-20, page 12, lines 4-6, and page 384, see NM_002111), 60/440,129 (see, page 7, lines 23-30, page 8, lines 5-11), and PCT US03/05028 (see pages 9, 10, 14, 20-22, 23, 27-31).

In addition, claims 13, 14, 15, 18, 19, and 20 have been amended to clarify that 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of the specified purine or pyrimidine nucleotides has the specified modification. Support for the amendment is found in the specification at, for example, pages 33-34. Support is also found in the priority documents. See, e.g., U.S. Provisional patent application No. 60/440,129 (see, page 10, lines 10-17, page 15, lines 4-20, page 22, lines 1-9 and lines 25-30, page 23, lines 15-20, and page 25, lines 20-25). See, e.g., U.S. Provisional patent application Nos. 60/363,124 (see, page 10, lines 3-16 and page 11, lines 1-11). See, e.g., PCT US03/05028 (pages 20-22).

In addition, the claims have been further amended merely to correct dependencies and other matters of form.

New claim 33 depends from claim 1 and recites a nucleic acid molecule wherein additionally 1, 2, or 3 purine nucleotides in the sense strand are 2'-O-methyl nucleotides. Support for new claim 33 is found in the specification at, for example, pages 33-34. Support is also found in the priority documents. See, e.g., U.S. Provisional patent application No.60/440,129 (see, page 25, lines 20-25, page 10, lines 13-17). See, e.g., PCT US03/05028 (pages 20-22). See, e.g., U.S. Provisional patent application No.60/363,124 (see, pages 10-11).

New claim 34 depends from claim 1 and recites a nucleic acid molecule wherein the antisense strand, sense strand, or both the antisense strand and sense strand include a 3′-overhang of 1-3 nucleotides. Support for new claim 34 is found throughout the specification and in particular at, for example, page 12. Support is also found in the priority documents. See, e.g., U.S. Provisional patent application No.60/363,124 (see, pages 4 and 9).

New claim 35 depends from claim 34 and recites a nucleic acid molecule wherein the nucleotides of the 3′-overhang are chemically modified with one or more phosphorothioate internucleotide linkages, 2′-O-methyl ribonucleotides, 2′-deoxy-2′-fluoro ribonucleotides, 2′-deoxy ribonucleotides, universal base nucleotides, 5-C-methyl nucleotides, inverted deoxyabasic moieties or a combination thereof. Support for new claim 35 is found throughout the specification and in particular at, for example, page 20.

Support is and in particular at also found in the priority documents. See, e.g., U.S. Provisional patent application No.60/363,124 (see, pages 4 and 9).

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

A complete listing of all the claims, in compliance with the revised amendment format, is shown above.

Priority

The Office accords the instant application a priority date of February 20, 2004, which is the filing date of the application. The Office did not accord the instant application the benefit of the earlier priority applications because it alleges that the claim element reciting wherein about 100% of the nucleotide positions in one or both strands of the nucleic acid molecule are chemically modified is not supported by the specification or the claims of the priority applications.

Contrary to the Office's allegation, the instant claims are fully supported by the priority applications, including PCT/US03/05028 and 60/363,124 (to which PCT/US03/05028 claims priority). For example, U.S. provisional application 60/363,124 teaches GenBank Accession Number NM_002111 in Table III, at page 384. Support for other elements of claim 1 are found at, for example, pages 5, 7, 8, 9, 10, 12, 35, 36, 55-57, and Figures 4-10 and Table I (pages 70-78). Support for the dependent claims as amended are found at, for example, pages 26-27 (claim 3), pages 9, 10, 11, 35, 36, 55-57, and Figures 4-10 and Table I (pages 70-78) (claims 13-15, 18-20, and 33), pages 5, 7, 8, 10, 11, 13, 14, and 40 (claims 16 and 17), pages 5, 9, 10, and 11 (claim 21), pages 8-9 (claim 30), page 18 (claim 31), pages 4, 5, 9, 12, 31, and 60 (claims 34 and 35). Additional support is found in Figures 3-10 and the examples.

Applicant submits that the claim element reciting "about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2′-O-methyl, 2′-deoxy-2′-fluoro, 2′-deoxy, phosphorothioate and deoxyabasic modifications" is fully supported by U.S. provisional application 60/363,124. See, for example, pages 10-11 where the specification teaches that the nucleic acid molecules can have 1-10 phosphorothioate internucleotide linkages in both strands, one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands. The specification also teaches that the nucleic acid molecules can have 1-10 phosphorothioate internucleotide linkages in both strands, 1-10 nucleotides of the sense and/or antisense strands chemically modified with 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands. Based on the size of the molecule (18-27 nucleotides), Applicant submits that one skilled in the art would realize that the specification teaches that about 50-100% of the nucleotides in the antisense and sense strands are chemically modified. Furthermore, Applicant provides numerous examples of specific chemically modified nucleic acid molecule having about 50-100% chemical modifications in Table I, pages 55-57, and Figures 3-10. For example, nucleic acid molecule 28254/28256 has about 50% chemical modifications on both strands. Other examples include 27653 and 27658 (100% chemical modifications); 27655, 27654, 27658, 28254, 27661, 27659, 27660, 27660, and 28244 (50-80% chemical modifications). See Table I for numerous other examples of nucleic acid molecules having about 50-100% chemical modifications.

The instant application claims priority to and incorporates by reference PCT/US03/05028 in its entirety, which application claims priority to and incorporates by reference 60/363,124 in its entirety. Thus, the instant application properly claims priority to the 60/363,124 application. As discussed above, both the PCT/US03/05028 and 60/363,124 applications fully support the instant claims. Applicant respectfully submits

that the instant invention is entitled to a priority date of at least March 11, 2002, the filing date of the 60/363,124 application.

Specification

The Office has objected to the specification because allegedly pages 49-69 are missing. To clarify, pages 49-69 are present in the originally filed application, except that they were inadvertently inserted after page 169. Applicant has submitted a replacement specification with the pages in the correct chronological order. Applicant respectfully requests entry of the substitute specification and withdrawal of the objection to the specification.

Claim Objections

Claim 18 was objected to because it does not have a period at the end of the claim. Claim 18 has been amended to include a period at the end of the claim. Applicants respectfully request withdrawal of the objection.

Obviousness-Type Double Patenting Rejection

Claims 1, 3, 13-21 and 30-32 were provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 3, 13-21 and 30-31 of copending application 10/824036 in view of Rana (US 2005/0020521). Without acceding to the merits of the rejection, Applicant will consider filing a terminal disclaimer at the appropriate time.

35 U.S.C. § 103 Rejections

Claims 1, 3, 13-15, 18-21 and 30-32 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden *et al.*, Rana et al. (US 2005/0020521), Hammond, and Vickers (J. Biol. Chem., 2003), Bass (Nature 2001) and evidenced by Caplan (Expert Opin. Biol. Ther., 2003). Claim 32 has been canceled, thus rendering the rejection moot as applied to this claim. Applicants respectfully traverse the rejection as it applies to amended claims 1, 3, 13-15, 18-21, and 30 and 31.

The Office relies on Hayden to teach the use of antisense targeted to HD gene. However, Hayden *et al.* teach a single stranded antisense molecule targeted to an HD gene. Hayden does not teach or suggest a chemically modified nucleic acid molecule comprising a distinct sense strand and an antisense strand. Furthermore, it does not teach a nucleic acid molecule comprising a structure where the antisense strand comprises nucleotide sequence of 18 to 27 nucleotides that is complementary to a human huntingtin (HD) RNA comprising SEQ ID NO: 3578.

The Office relies on Hammond, Vickers, and Bass to teach generally RNAi technology. However, these references merely teach general RNAi and dRNA; none of these references teach siRNA targeted to HD RNA, much less chemically modified siRNA.

The Office relies on Rana to teach chemical modifications of siRNA. However, Applicant submits that Rana is not prior art to the instant application. For reasons discussed above, the instant application should be accorded a priority date of March 11, 2002. Even assuming that the priority documents disclose the subject matter of Rana US 2005/0020521, the earliest possible priority date is September 25, 2002, that is, after the priority date of the instant specification.

The Office argues that it would have been obvious to one skilled in the art to make an siRNA molecule as taught by Hammond, Vickers and Rana to target a gene encoded by HD, as taught by Hayden and would have further been obvious to make a chemically modified siRNA as taught by Rana. The Office argues that one would have been motivated to make such a molecule because Hayden teaches that HD protein is involved in neurodegenerative diseases and Hammond and Vickers teach that RNAi is more potent than antisense. The Office further argues that one would have a reasonable expectation of success because Hayden teach that antisense can be targeted to HD and regulate gene expression and Hammond and Vickers teach that RNAi is more potent than antisense. One would also have a reasonable expectation of success introducing 100% chemical modifications because Rana teaches that chemically modified siRNA is more stable than unmodified siRNA and capable of eliciting RNAi. The Office finally argues

that one skilled in the art would have a reasonable expectation of success because chemical modifications of oligonucleotides were known in the art at the time of filing and one would expect that such modifications would benefit siRNA because they were shown to modify antisense and ribozymes.

Under 35 U.S.C. § 103(a), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

None of these references, alone or in combination, render obvious the presently claimed nucleic acid molecules because the cited references do not teach or suggest all of the claim elements. Hayden does not teach siRNA targeted to HD RNA, much less HD RNA comprising SEQ ID NO: 3578. It also does not teach chemically modified siRNA. Hammond, Vickers, and Bass merely teach RNAi in general and provide no teaching or motivation to target HD. They also do not teach siRNA, nor do they teach chemical modification of siRNA. Rana is not prior art to the instant application.

Thus, none of these references, either alone or in combination, teach a nucleic acid molecule having the recited elements. In particular, none of the references, either alone or in combination, teach a nucleic acid molecule having the following features: (1) it comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; (2) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length; (3) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a human huntingtin (HD) RNA sequence comprising SEQ ID NO: 3578; (4) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human HD RNA; (5) about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically

modified with modifications independently selected from the group consisting of 2′-O-methyl, 2′-deoxy-2′-fluoro, 2′-deoxy, phosphorothioate and deoxyabasic modifications; and (6) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2′-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2′-deoxy-2′-fluoro pyrimidine nucleotides.

Despite the lack of teaching in the cited references, the Office suggests that it would have been obvious to make double stranded nucleic acid molecules having chemical modifications with a reasonable expectation of success because chemical modification of oligonucleotides, adding stability and specificity to the oligonucleotides, were known in the art and would be expected to benefit siRNA because they had been shown to benefit antisense.

However, Applicant submits that antisense and ribozyme art is not analogous art to siRNA technology and should not be the basis for an obviousness rejection. Any reference or general knowledge cited to demonstrate obviousness must be analogous art. The reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992).

Antisense and ribozyme art is not reasonably pertinent to chemically modified siRNA molecules that target HD RNA. Antisense molecules are substantially single-stranded prior to interacting with their target, while siRNA is almost completely in a duplex form; it is well known to those skilled in the art that single-stranded nucleic acid is more susceptible to nuclease attack than is double-stranded nucleic acid. Antisense molecules will tolerate substantial 5' and 3' terminal modifications; in contrast the activities of siRNAs are almost completely destroyed by attaching modifications to the 5' end of the antisense strand of the siRNA. The activity of an antisense molecule is destroyed by modifications that alter the DNA-like structure at the core of molecule. It was not clear in 2001 whether the siRNA duplex would need to maintain an RNA-like structure or whether other structures would be permitted.

Likewise, ribozymes are non-analogous art to siRNA. Ribozymes are substantially single-stranded prior to interacting with their target, while siRNA is almost completely in duplex form. It is well known to those skilled in the art that single-stranded nucleic acid is more susceptible to nuclease attack than is double-stranded nucleic acid. Additionally, ribozymes will tolerate substantial 5' and 3' terminal modifications. In contrast, the activity of siRNA molecules is almost completely destroyed by attaching modifications to the 5' end of the antisense strand of the siRNA. Also, unlike siRNA molecules, ribozymes must form a complex RNA secondary structure to be active.

At the priority date of the present application, those of ordinary skill in the art understood that there were different structural features of nucleic acids required for activity in each of ribozyme and siRNA technologies because the mechanism of action of these nucleic acids differed in each. Significantly, the mechanism of siRNA had not yet been explored to the extent that one of ordinary skill in the art understood or could predict the effect of various types and positions of chemical modifications on the activity of a double stranded nucleic acid molecule.

For the reasons discussed above, the cited references, alone or in combination, do not render obvious the instantly claimed methods of synthesizing chemically modified nucleic acid molecules. Accordingly, Applicant respectfully requests withdrawal of the 35 USC §103 Rejection.

Claims 1, 3, 13-21, and 30 -32 stand rejected under 35 U.S.C. 103(a) as being obvious over Hayden *et al.*, Rana (US 2005/0020521), Hammond *et al.*, and Vickers (J. Biol. Chem., 2003) and evidenced by Caplan (Expert Opin. Biol. Ther., 2003) in further view of Matulic-Adamic *et al.* Claim 32 has been canceled, thus rendering the rejection moot as applied to this claim. Applicants respectfully traverse the rejection as it applies to amended claims 1, 3, 13-21, 30 and 31.

Hayden *et al.*, Rana (US 2005/0020521), Hammond *et al.*, and Vickers (J. Biol. Chem., 2003) are relied on for the teachings discussed above. However, Hayden *et al.*, Rana (US 2005/0020521), Hammond *et al.*, and Vickers (J. Biol. Chem., 2003) fail to render obvious the claimed invention for the reasons set forth above.

Matulic-Adamic is relied on for teaching a terminal cap moiety at the 5'-end, 3'-end or both ends, including an inverted deoxyabasic moiety. However, Matulic-Adamic fails to cure the deficiencies of Hayden *et al.*, Rana (US 2005/0020521), Hammond *et al.*, and Vickers (J. Biol. Chem., 2003). Matulic-Adamic teach chemical modification of ribozymes. For the reasons discussed above, ribozyme art is non-analogous art to the claimed invention. Those of ordinary skill in the art would have understood that there were different structural features of nucleic acids required for activity in each of ribozyme and siRNA technologies because the mechanism of action of these nucleic acids differed in each.

For the reasons discussed above, the cited references, alone or in combination, do not render obvious the instantly claimed methods of synthesizing chemically modified nucleic acid molecules. Accordingly, Applicant respectfully requests withdrawal of the 35 USC §103 Rejection.

Claims 1, 3, 13-21, and 30-32 stand rejected under 35 U.S.C. 103(a) as being obvious over Davidson *et al.*, Rana (US 2005/0020521), and Matulic-Adamic *et al* and evidenced by Caplan (Expert Opin. Biol. Ther., 2003). Claim 32 has been canceled, thus rendering the rejection moot as applied to this claim. Applicants respectfully traverse the rejection as it applies to amended claims 1, 3, 13-21, 30 and 31.

Applicant submits that Rana is not prior art for the reasons set forth above. Davidson is also not prior art to the claimed invention. The earliest possible priority date for Davidson is August 5, 2002, which is after the March 11, 2002 priority date that should be accorded the instant invention. Matulic-Adamic fails to teach or suggest the claimed invention for the reasons previously set forth.

For the reasons discussed above, the cited references, alone or in combination, do not render obvious the instantly claimed methods of synthesizing chemically modified nucleic acid molecules. Accordingly, Applicant respectfully requests withdrawal of the 35 USC §103 Rejection.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,
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